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From Pseudohypoparathyroidism to inactivating PTH/PTHrP Signalling Disorder (iPPSD), a novel classification proposed by the European EuroPHP-network

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Abbreviations: PHP: pseudohypoparathyroidism, PTH: parathyroid hormone, PTH1R: PTH receptor type 1, PTHrP: PTH related peptide, Gsa: alpha subunit of stimulatory G proteins, PHP1: PHP type 1, PHP2: PHP type 2, PHP1A: PHP type 1A, PHP1C: PHP type 1C, PHP1B: PHP type 1B, ACRDYS1: acrodysostosis type 1, ACRDYS2: acrodysostosis type 2, AHO: Albright Hereditary Osteodystrophy, PPHP: pseudopseudohypoparathyroidism, DMR: differentially methylated regions, AD-PHP1B: autosomal dominant PHP1B, LOI: loss of imprinting, LOM: loss of methylation, UPD: uniparental disomy PKA: protein kinase A, PDE: phosphodiesterase, HTNB: Hypertension and Brachydactyly Syndrome, iPPSD: Inactivating PTH/PTHrP Signalling Disorder, BDE: Brachydactyly type E, GHRH: Growth Hormone Releasing Hormone, IUGR: Intra Uterine Growth Retardation, ICR: Imprinting Control Region, POH: Progressive Osseous Heteroplasia

Abstract

Objective: Disorders caused by impairments in the parathyroid hormone (PTH) signalling pathway are historically classified under the term pseudohypoparathyroidism (PHP), that encompasses rare, related but highly heterogeneous diseases with demonstrated (epi)genetic causes. The actual classification is based on the presence or absence of specific clinical and biochemical signs together with an *in vivo* response to exogenous PTH and the results of an *in vitro* assay to measure Gsa protein activity. However, this classification disregards other related diseases like acrodysostosis (ACRDYS) or Progressive Osseous Heteroplasia (POH), as well as recent findings of clinical and genetic/epigenetic background of the different subtypes.

Therefore, the EuroPHP network decided to develop a new classification that encompasses all disorders with impairments in PTH and/or PTHrP cAMP-mediated pathway.

Design and Methods: Extensive review of the literature was performed. Several meetings were organised to discuss about a new, more effective and accurate way to describe disorders caused by abnormalities of the PTH/PTHrP signalling pathway.

Results and Conclusions: After determining the major and minor criteria to be considered for the diagnosis of these disorders, we proposed to group them under the term «inactivating PTH/PTHrP signalling disorder», (iPPSD). This terminology: 1) defines the common mechanism responsible for all diseases, 2) does not require a confirmed genetic defect, 3) avoids ambiguous terms like “pseudo”, 4) eliminates the clinical or molecular overlap between diseases. We believe that the use of this nomenclature and classification will facilitate the development of rationale and comprehensive international guidelines for the diagnosis and treatment of iPPSDs.

Introduction

Pseudohypoparathyroidism (PHP) encompasses a group of rare, related, highly heterogeneous and deeply impairing disorders characterized by end-organ resistance to the action of parathyroid hormone (PTH) and in most instances associated with a demonstrated (epi)genetic component (1–3). PHP is historically the first hormone resistance syndrome described by Fuller Albright and colleagues in 1942 (4).

A better understanding of the PHP pathophysiology followed the identification of the PTH receptor (PTH1R) and its signal transduction pathway (Figure 1) (5,6). PTH1R, through its activation by two ligands, the PTH and the PTH related peptide (PTHrP), regulates skeletal development, bone turnover and mineral ion homeostasis. In the kidney, binding of PTH to PTH1R stimulates the production of 1,25 dihydroxy vitamin D3, and inhibits phosphate reabsorption in the proximal tubule, while it increases calcium reabsorption in the distal nephron. In the growth plate, PTHrP promotes endochondral ossification, through the binding to PTH1R (7).

The Blomstrand chondrodysplasia (OMIM # 215045), a lethal form of dwarfism (8), was the first disorder associated with biallelic loss-of-function mutations of the *PTH1R* gene (9). Subsequently, one report has described a milder phenotype in living children affected with Eiken disease (OMIM # 600002), short stature, elevated PTH and mutations of *PTH1R* (10,11).

A defect in the response of the proximal renal tubule to PTH is the hallmark of all forms of PHP. It manifests as hypocalcemia, hyperphosphatemia and elevated circulating levels of PTH in the absence of vitamin D deficiency (5,7,12).

PTH receptor couples with the stimulatory G protein (Gsa), leading to cAMP formation. Renal tubular response to exogenously administered PTH through measurement of serum and urinary cAMP levels, permits the differentiation of PHP type 1 (PHP1), in which a blunted cAMP response is observed, from PHP type 2 (PHP2), where cAMP increase is conserved but the phosphaturic response is deficient (13). To date, only a handful of PHP2 cases have been reported, and the molecular defect responsible for this variant is still unknown. It has also been hypothesized that PHP2 could either be an acquired defect secondary to vitamin D deficiency (14), as calcium and vitamin D supplementation resulted in normalization of the phosphaturic response to

PTH in some patients (14,15) or due to defects downstream the Gsa protein, as seen in patients with acrodysostosis type 1 (ACRDYS1) (16).

In 1980, deficiency in the Gsa protein activity in erythrocytes extracted from patients affected with PHP1 was demonstrated *in vitro* (17,18). For years, this bioassay allowed the diagnosis of PHP, and contributed to PHP subclassification (see below).

PHP type 1 (PHP1) is further subdivided based on the presence (PHP1A and PHP1C; OMIM #103580 and #612462, respectively) (6,17–19) or absence (PHP1B; OMIM #603233) (6,20) of Albright Hereditary Osteodystrophy (AHO) (Table 1). AHO is a clinical entity initially described together with PHP in 1942, which encompasses heterogeneous clinical findings such as brachydactyly, rounded face, short stature, stocky build and subcutaneous ossifications (4,21,22). Additional features that may not directly relate to AHO, yet extensively associated with PHP1A individuals, include obesity, varying degrees of intellectual disability and resistance to several hormones, including TSH, GHRH and calcitonin (23–28) . The subcategory of PHP1C has all the characteristics of PHP1A, except that Gsa activity in erythrocytes was found comparable to controls (29,30).

Interestingly, patients showing the physical features of AHO without any evidence of PTH resistance were also described by Albright and colleagues ten years after their first report of PHP (21). This new syndrome, named pseudo-pseudohypoparathyroidism (PPHP; OMIM #612463) may be present either in kindreds with PHP or as an isolated defect. It is possible that the "bone phenotype" observed in AHO is largely mediated by the resistance to PTHrP at the growth plate during fetal and post-natal growth (31).

In 1990 the first heterozygous inactivating mutation in the gene coding for Gsa (*GNAS)*, responsible for PHP1A, was described (32). Since then, several Gsa-coding mutations have been identified in all of its 13 exons with different frequency, with a detection rate of about 70% (33–39). Cases of deletions of 20q, including part or the whole *GNAS* gene, and an inversion at *GNAS* have been recently reported (40–44). Remarkably, similar mutations when paternally inherited, or occurring *de novo* on the paternal allele of *GNAS* may lead to PPHP or to Progressive Osseous Heteroplasia (POH, OMIM #166350), a disorder characterized by heterotopic ossifications expanding into deep muscles and connective tissues (45,46).

GNAS is a locus encoding several transcripts through alternative splicing. In most tissues, except for Gsa, the *GNAS* transcripts are of monoallelic origin due to the control of their expression by parent-specific differentially methylated regions (DMRs) (Figure 2) (47). In thyroid, pituitary gland and most likely in the proximal tubule (36), Gsa is predominantly expressed from the maternal allele through a yet unexplained mechanism (48,49). In the early 2000, the molecular defect of PHP1B was characterized. The most consistent defect common to all PHP1B patients is a paternal-specific pattern of cytosine methylation within the maternal *GNAS A/B*: transcriptional start site (TSS)-DMR (*GNAS A/B:*TSS-DMR; previously known as exon A/B or 1A) which could lead to a decreased expression of Gsa in the renal proximal tubules, hence PTH resistance (50). Fifteen to 20% of the PHP1B cases present familial history with an autosomal dominant mode of inheritance (AD-PHP1B) through the maternal lineage. Most AD-PHP1B show loss of imprinting (LOI) limited to the *GNAS A/B*:TSS-DMR (more precisely a loss of methylation [LOM]) associated with deletions on the maternal allele of *cis*-acting control elements within *STX16* or *NESP55* (51–55), although other maternally inherited deletions have been identified affecting all four DMRs (*GNAS-NESP*:TSS-DMR, *GNAS-AS1*:TSS-DMR, *GNAS-XL*:Ex1-DMR and *GNAS A/B:*TSS-DMR) (56–58).

The remaining cases of PHP1B are sporadic. They present with broad LOI at *GNAS*, including the *GNAS A/B*:TSS-DMR. The molecular basis of this broad LOI is yet to be identified, with an exception of less than 10% of the patients who are affected by paternal complete or segmental uniparental disomy (UPD) of the chromosome 20, comprising the *GNAS* locus (59–63).

To summarize, the existing classification of PHP (Table 1) is based on the following criteria, 1-presence or absence of AHO differentiates **PHP1A/PHP1C** from **PHP1B**, 2-presence or absence of hormonal resistance differentiates **PHP1** from **PPHP**, 3-*in vivo* response to exogenous PTH as for nephrogenic cAMP synthesis and phosphaturia seperates **PHP1** from **PHP2**, and 4-*in vitro* assay measuring the Gsa protein activity from erythrocyte membranes, differentiates between **PHP1A** and **PHP1C.**

As described above, the existing PHP classification does not include molecular defect as a criterion and fails to stratify PHP and AHO as well as include conditions such as acrodysostosis, POH and PTH1R-related chondrodysplasia. In this manuscript, we therefore propose to review the rationale of this nomenclature and recommend a novel classification for disorders impairing the PTH/PTHrP signalling pathway.

Methodology

The EuroPHP network met on three different occasions (October 2014, May 2015, November 2015) to discuss and agree on a novel classification. The aims of these meetings were 1- to identify the limitations in the current PHP classification, 2- to formulate mandatory criteria for the new classification, 3- to propose a comprehensive definition gathering all the disorders, 4- to analyse the classifications used in other genetic/epigenetic conditions, 5- to generate a novel classification. The methodology comprised of a thorough review of the current literature to facilitate comparison and form basis for the proposal of a new classification.

We have carefully considered a series of classifications proposed for various rare genetic/epigenetic disorders, including the reporting manuscripts that were taken into consideration for the design of a novel classification (summarized in Table 2). In brief, methodologies were similar. A group of experts in the field identified the deficiencies in the existing classification/terminology and the need for an update. Subsequently agreement on a novel terminology and classification was reached and reported (64–70).

Challenges and limitations of the current classification

Recent clinical and molecular data gathered for these complex disorders have questioned the distinction of the different PHP and AHO subtypes in the existing classification (Table 1). We have selected the following limits of the current classification.

1- In a subset of patients with PHP1A and varying degree of AHO, LOI of *GNAS* identical to that of PHP1B has been reported, suggesting a molecular and clinical overlap between the two subtypes (71); further confirmed (72–75).

2- PHP1B patients present with a moderate reduction of Gsa activity in erythrocyte membranes, reminiscent -yet less severe- to that observed in patients with PHP1A and PPHP (76).

3- Recently, mild resistance to PTH was described in patients affected with PPHP, carrying a paternal *GNAS* mutation (77), showing that the hormonal resistance is not only associated with maternally inherited *GNAS* mutations.

4- Different molecular defects have been identified in patients with PHP1C, i.e. LOI at *GNAS* and four loss-of-function mutations in the *GNAS* carboxyl-terminus leading to a conserved adenylyl cyclase receptor-independent activation but disrupted receptor-mediated activation (29,30,78).

6- Paternal *GNAS* mutations associated with Progressive Osseous Heteroplasia are usually truncating mutations (79), yet they are identical to those found in

families with PHP1A and/or PPHP (45). Also noteworthy, is that a fraction of POH patients exhibits some of the typical AHO features and, conversely, some PHP1A patients carrying mutations on the maternal allele, present with progressive deepening heterotopic ossifications. The hypothesis that POH should be considered as a form of PPHP is therefore debated (80,81).

7- Heterozygous mutations in *PRKAR1A* -coding for the regulatory subunit of the protein kinase A (PKA)- and *PDE4D* -coding for phosphodiesterase type 4- have been found in patients with acrodysostosis (16,82,83). Acrodysostosis refers to a heterogeneous group of rare diseases characterized by skeletal dysplasia and characteristic features, including brachydactyly, facial dysmorphism and, in some cases, mental retardation (84–88). Acrodysostosis differs from PHP by more generalized osseous abnormalities (87,89). Resistance to PTH and/or TSH is present in about 60-70% of acrodysostosis patients with a *PRKAR1A* mutation, while, in case of a *PDE4D* mutation, such hormone resistances are found only in a smaller subset of 10-20%. Interestingly, few patients bearing a *PRKAR1A* mutation have been described in patients with a phenotype indistinguishable from PHP1A (90,91).

8- Heterozygous mutations in *PDE3A* have been identified in patients affected with hypertension and brachydactyly type E (Hypertension and Brachydactyly Syndrome (HTNB): OMIM #112410) (92).

9- Disorders associated with an impaired function of *PTH1R*, i.e. the Blomstrand and Eiken skeletal dysplasia, are currently not included in the classification.

Over the past two decades it became obvious that clinical features such as AHO or *in vitro* assays such as Gsa bioactivity fail to differentiate between PHP subtypes. In addition, mutations of genes different from *GNAS* have been shown to lead to PTH and/or PTHrP resistance and *GNAS* mutations might trigger diseases different from PHP/PPHP (i.e. POH). These disorders are not encompassed by the current classification system.

For all these reasons, different independent studies from the authors of the present paper, as well as the "EuroPHP network" concluded and agreed that a uniform terminology is required to create a functional working classification that reflects the current knowledge of the diseases (29,93,94).

Terminology

We propose the term of «inactivating PTH/PTHrP signalling disorder», abbreviated as iPPSD, which encompass all disorders related to this pathway. We also propose that numbering will allow for both clinical features as well as molecular and genetic findings to be included. The advantages of this terminology are as follows: 1- it describes the common mechanism responsible

for the diseases, 2- it does not require a confirmed genetic defect, 3- it avoids the ambiguous term like “pseudo”, 4- it eliminates the clinical or molecular overlap between diseases and 5- it is flexible to incorporate new evolving information.

We recognize that the nomenclature «inactivating PTH/PTHrP signalling disorder» might be initially difficult for patients and caregivers to remember. It would therefore be helpful to rely on the abbreviation iPPSD. Equally the former terms “pseudohypoparathyroidism” and “pseudopseudohypoparathyroidism” were also long and challenging to use for communication. PTH/PTHrP specific pathway was deliberately included in the name of the classification to avoid the misperception with disorders resulting from the inactivation of G protein-coupled receptors, i.e. inactivating mutations in the TSH receptor or in the FSH receptor. All nomenclature based on the cAMP signalling were carefully considered and rejected due to their generic nature.

Identification of mandatory criteria for the new classification

Basis for the newly proposed classification of iPPSD are:

- To provide patients with an unambiguous diagnosis;

- To base nomenclature on pathophysiology, i.e. the PTH1R/Gsa/cAMP/PKA pathway, and a standardized diagnostic pathway;
- To formulate basis to develop new therapeutic approaches;
- To be sufficiently flexible and adaptable to include emerging clinical and molecular information;
- To be simple and usable for the caregivers.

It is therefore of significant importance to define the category of iPPSD a patient belongs to, based on the characterization of clinical/biochemical criteria, to facilitate a definive diagnosis and, if possible, through molecular analysis, a more specific denomination within the classification.

We suggest three key clinical features as major criteria for the diagnosis of iPPSD. The proposed major criteria have minimum or no overlap with other conditions due to different mechanisms (see Table 3, especially for the differential diagnoses).

We also propose a list of minor criteria that are associated with iPPSD. These are less specific to iPPSD compared to major criteria and can occur in other

clinical conditions. Therefore, minor criteria need to be combined with one or more major criteria to establish the diagnosis of iPPSD.

Major criteria

1. PTH resistance

The hallmark of inactivating PTH/PTHrP signalling disorders is the resistance of the renal proximal tubule to the action of PTH. All genetic defects leading to a deficient PTH1R signalling in the kidney will therefore be named iPPSD.

2. Ectopic ossifications

Ectopic ossifications are superficial, subcutaneous nodules, defined as ectopic bone formation in the adipose or dermal tissue. Progressive Osseous Heterotopic calcifications often begin in the dermal and subcutaneous tissues and later progress to the deeper tissues, such as muscles and tendons. In children, ectopic ossifications are highly suggestive of an inactivating *GNAS* mutation, i.e. iPPSD.

3. Brachydactyly

Brachydactyly refers to shortening of fingers, toes or both. Brachydactyly type E (BDE, OMIM #113300) encompasses variable shortening of the metacarpals/metatarsals, often with the involvement of phalanges (see Figure 3). It can either present in isolation or as part of a genetic disorder, most of which are included among iPPSD (95).

Brachydactyly can be challenging to identify in early childhood, and tends to become more evident during early puberty. Brachydactyly can be overlooked when all bones are short as in acrodysostosis since early childhood.

While PTH resistance and ectopic ossifications are considered major criteria for iPPSD, brachydactyly is less specific and should therefore be combined with at least one major or two minor criteria to trigger the diagnosis of iPPSD.

Minor criteria

1. Thyroid Stimulating Hormone (TSH) resistance

In iPPSD, TSH resistance is often mild and characterized by elevated TSH levels associated with free thyroxine (T4) levels in a normal or low-normal reference range. This occurs in the absence of goitre and markers of autoimmune disease (26,27). TSH resistance can sometimes be the first detected sign of iPPSD, especially in countries where screening for congenital hypothyroidism is routinely performed (96).

2. Other hormone resistances

Very few other hormone resistances have been demonstrated so far. Resistance to growth hormone releasing hormone (GHRH), leading to growth hormone deficiency, is the most frequent additional resistance found in PHP1A, affecting as many as 60% of patients (97–99). Calcitonin resistance has been described without clinical features in patients affected with PHP1A (27).

Elevated follicular stimulating hormone (FSH) and luteinizing hormone (LH) levels were reported both by us and Namnoum et al (78,100). Glucagon and epinephrine resistances were demonstrated in patients with features of PHP and low Gsa bioactivity through *in vivo* testing (6,101).

3. Motor and cognitive retardation or impairment

Psychomotor and cognitive alterations have been described in about 40 to 70% of the patients with a maternal coding mutation of *GNAS* (25,34), as well as in some patients affected with acrodysostosis (83,85,86). Psychiatric manifestations have also been reported in these patients (102). Patients with paternal mutations of *GNAS* or epigenetic modifications of the *GNAS* DMRs seem unaffected (25,63).

4. Intra-uterine and post-natal growth retardation

Intra-uterine growth retardation (IUGR) has been frequently observed in both maternal and paternal inherited inactivating *GNAS* coding mutations. However, IUGR is more pronounced in patients harbouring mutations on the paternal *GNAS* allele, mainly when affecting *GNAS* exon 2-13 mutations, compared to patients with *GNAS* exon 1/intron 1 mutations (103). IUGR has also been described in acrodysostosis with mutations in *PRKAR1A* or *PDE4D*, and in patients with mutations in *PDE3A* (16,82,90,92). A LOI at the maternal *GNAS A/B:* TSS-DMR has been associated with increased intra-uterine growth (104).

Post-natal growth retardation is a frequent sign in PHP1A and acrodysostosis. Growth hormone deficiency and premature closure of the epiphysis result in short stature (16,82,97,105). Growth retardation has also been observed in PHP1B, although only in exceptional cases (71,74), and in patients with Eiken dysplasia (10).

5. Obesity/overweight

Obesity or overweight may be the most nonspecific minor sign, however it occurs very frequently in disorders with an impaired PTH/PTHrP signalling pathway and may help to differentiate between the different subtypes. Growth hormone deficiency, impaired lipolytic response of epinephrine (101), or decreased resting energy expenditure (106) contribute to the development of obesity in patients with mutations on the maternal allele of *GNAS* (23,107). Obesity is also a frequent feature in patients affected with acrodysostosis (16,90,108).

6. Flat nasal bridge and/or maxillar hypoplasia and/or round face

Elements of facial dysmorphism have been associated with acrodysostosis (flat nasal bridge and/or maxillar hypoplasia) or with PHP1A (round face) (4,86).

Diagnosis of iPPSD

We propose that a minimum of one of the major criteria is mandatory for the clinical diagnosis of iPPSD. PTH resistance or ectopic ossifications may lead to the diagnosis of iPPSD with or without the presence of minor criteria. However, brachydactyly type E (BDE) should be associated with at least one major or two minor criteria to suggest iPPSD, as it is a common feature of several other diseases and syndromes (Table 3).

The known molecular causes of PTH/PTHrP signalling disorders are:

- Inactivating mutations of *PTH1R*;
- Inactivating heterozygous mutations in the coding sequence of *GNAS*-Gsa*;*
- Methylation changes of the DMRs of *GNAS* caused by
  - -deletions or duplications at ICRs (*STX16; NESP; GNAS*-AS1);
  - -paternal UPD of chromosome 20q;
  - -unknown mechanism(s);
- Heterozygous mutations of *PRKAR1A*;
- Heterozygous mutations of *PDE4D*;
- Heterozygous mutations of *PDE3A*.

In contrast to the former diagnostic classification based solely on the phenotype, once iPPSD has been identified (using criteria described Table 3),

we propose to further subtype iPPSD based on the underlying molecular (epi)genetic defect. Therefore, the term iPPSD will refer to the pathophysiology of the PTH/PTHrP signalling abnormalities, while the number will refer to the underlying molecular mechanism (responsible for the pathology). We have numbered iPPSD subtypes starting with *PTH1R* mutations.

The novel classification of iPPSD

The European PHP-network proposes the following classification (Figure 4):

- iPPSD: clinical/biochemical diagnosis based on the major/minor criteria as defined above, in the absence of genetic investigation;
- iPPSD1: loss of function mutation in *PTH1R* ;
- iPPSD2: loss of function mutation in Gsa;
- iPPSD3: methylation change(s) at one or more *GNAS* DMRs, associated with or without a genetic (deletion) or cytogenetic (UPD) defect;
- iPPSD4: *PRKAR1A* mutation;
- iPPSD5: *PDE4D* mutation;
- iPPSD6: *PDE3A* mutation;
- iPPSDx: lack of genetic/epigenetic defect identified following molecular investigation of known genes described above;

- iPPSDn+1: the identification of a novel gene/molecular defect will lead to a disease named iPPSD7, then 8 and so on.

iPPSD3 encompasses all disorders associated with changes in the methylation patterns of the DMRs of *GNAS*, including UPD(20)pat and deletion within *STX16, NESP,* etc. Of most significance, is the common mechanism shared by these patients, i.e. the LOM at the *GNAS A/B*:TSS-DMR. Grouping them under iPPSD3 highlights this common mechanism. Secondly, we anticipated the difficulties in integrating the multiplicity of the epigenetic mechanisms within the classification system as this adds no further diagnostic value. However, the further specification of the epigenetic defect can remain part of a private exchange between the molecular laboratory, the patient and his/her physician. We recommend the use of Arabic numerals to avoid the confusion with letters (II with the number 11 for example).

The advantages of this new nomenclature are: 1- it stratifies the disorders into clusters caused by the same mechanism, 2- it is flexible and open to accommodate new defects to be discovered in the future and 3- it simplifies the concept of the overlapping disorders under a single umbrella.

This classification however bears some limitations. We deliberately did not include the parental origin of the genetic/epigenetic defect, although some iPPSD are imprinting disorders -namely iPPSD2 and iPPSD3- and their phenotypic expression depends on their parental inheritance. The main reason behind this being the association of PTH resistance and POH with both maternal and paternal inactivating *GNAS* mutations. Therefore, the mechanism of the two allelic *GNAS* mutations can be considered alike. However, in daily practice, the parental origin of the *GNAS* defect should be considered, particularly for genetic counselling. In fact, AHO and multiple hormone resistance including PTH resistance are largely associated with maternal *GNAS* coding defects, whereas, isolated AHO and/or POH are more often associated with paternal *GNAS* coding defects.

Another limitation of this classification is the inability to sub classify individuals with a pure clinical suspicion of iPPSD and lack of complete (epi)genetic testing. While such patients cannot be classified as iPPSDx or with a specific number, we recommend that they are classified as iPPSD.

The inclusion of the disorders involving the two main ligands of the PTH1R, i.e. hypoparathyroidism (109) and brachydactyly type E with short stature (mutations in *PTHLH* the gene encoding PTHrP (110,111)) to the classification may be argued. However, we decided to exclude them due to several other

487 issues such as, 1- their different biochemical pattern including low levels of PTH
488 responsible for hypoparathyroidism 2- the dramatic difference in the therapy
489 of hypoparathyroidism and defects in PTH1R signalling, respectively and 3- the
490 difference in research goals in the two disease groups.
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Perspectives

We believe that the use of the new nomenclature will facilitate a more straightforward approach to the diagnosis of iPPSD, increase awareness of the red-flag signs of PTH resistance, ectopic ossifications and brachydactyly type E. It would allow for the classification of patients into local catalogues used by the different healthcare organizations in a more homogenous way, and enable future observational and research studies in the field.

We strongly believe that too many denominations for similar diseases and patients with phenocopies (PHP, PPHP, POH, ACRDYS, TRPS, BDE, AHO) has diluted and dispersed research advance, adding undue complexity to the causative mechanism and proved challenging for the experts in building a global research network in the field.

Regular use of the classification in daily practice or for scientific purposes will allow appropriate amendments in the best interest of the patients.

While producing this novel nomenclature and classification, we have identified the need to 1) disseminate this alternative classification to be positively enriched by the clinical and scientific community, 2) validate the major/minor

criteria in a series of patients affected by different iPPSDs, and 3) develop international guidelines for the diagnosis and treatment of the iPPSDs in the near future.

Declaration of interest

All the authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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539 **Legends for figures**

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541 **Figure 1:** Schematic transduction of PTH1R/Gsa/cAMP/PKA pathway.

542 Upon ligand binding (PTH or PTHrP are mentioned on the figure), the receptor

543 (PTH1R) activates the G protein. Then the Gsa subunit triggers the activation of

544 the adenylate cyclase leading to cAMP synthesis. cAMP binds to the regulatory

545 1A subunits (R1A) of the PKA, the most common effector of cAMP.

546 Upon cAMP binding, the catalytic subunits (Cat) dissociate from the R1A

547 subunits, and phosphorylate numerous target proteins including CREB (cAMP-

548 responsive binding elements) and the phosphodiesterases (PDEs). CREB

549 activates the transcription of cAMP responsive genes. Intracellular cAMP is

550 then deactivated by PDEs, among which are PDE4D and PDE3A.

551 PTH1R: transmembrane convolutional black line; G protein: trimer α, β, γ;

552 cAMP: grey diamond; PKA: tetramer R1A (regulatory subunit 1A) and Cat

553 (catalytic subunit); phosphodiesterases: ovals PDE4D or PDE3A; DNA: scale bar.

554

555 **Figure 2**: The imprinted human *GNAS* locus (Hg19-chr20:57,414,795-

556 57,486,250), on chromosome 20, close to the *STX16* gene (Hg19-

557 chr20:57,226,309-57,254,5812) (source UCSC, Hg19). The

558 centromeric/telomeric orientation of the chromosome is indicated. The

maternal (NESP), paternal (AB, AS and XL) and biallelic (Gsa) transcripts are depicted as arrows. Maternal and paternal expressed transcripts are drawn above and below the horizontal line, respectively. Black boxes: coding exons; grey boxes: non-coding exons; arrows: transcription (direction and parental origin). The brackets delimit the imprinting control element deletions, which have been reported. *STX16* gene: full brackets: the recurrent *STX16* deletion of 3.3kb (38); large dotted brackets: the *STX16* deletion of 4.4 kb (39); small dotted brackets: the *STX16* deletion of 29,5kb (42). *GNAS* locus: full brackets: the 4.7kb and 4kb deletions removing the *NESP* exon and exons 3 and 4 of *GNAS-AS1* (40); large dotted brackets: the 4.2kb deletion removing exons 3 and 4 of *GNAS-AS1* (43); deletions of 40pb [*] and 33pb [#] in introns of *NESP* and *GNAS-AS1* (44); small dotted brackets: the *NESP* and *GNAS-AS1* deletion (41). Mat: maternal ; Pat: paternal ; cen: centromeric ; tel: telomeric.

Figure 3: Patterns of brachydactyly type E associated with iPPSD.

a-e, brachydactylies associated with coding mutations in the Gsa subunit of the G protein (iPPSD2). **f-g**, bone phenotype associated with the loss of imprinting at the *GNAS* locus (iPPSD3). **h-j**, brachydactylies associated with the molecular defect in *PRKAR1A* (iPPSD4) and *PDE4D* (iPPSD5). Note the phenotypic overlap between a, h, j, and b, c, g, i, respectively.

Figure 4: Schematic representation of the new classification proposed by the European PHP network.

According to the suggested new classification Blomstrand and Eiken chondrodysplasia, PHP type 1 & 2, PPHP, AHO, POH and acrodysostosis clinically/biochemically diagnosed without genetic investigation are named iPPSD; Blomstrand and Eiken chondrodysplasia due to PTHR1 inactivating mutations are named iPPSD1; PHP1A, PHP1C, PPHP and POH clinically diagnosed and characterized by Gsa inactivating mutations are termed iPPSD2; PHP1B clinically diagnosed and due to methylation changes at the *GNAS* DMRs is classified as iPPSD3; in the presence of acrodysostosis type 1 or *PRKAR1A* mutations, the disease is classified as iPPSD4. Acrodysostosis type 2 or *PDE4D* mutations are termed iPPSD5; *PDE3A* mutations are categorized as iPPSD6; patients lacking genetic or epigenetic defects at the known genes fall under the category of iPPSDx; any newly discovered genetic/molecular defects will be labelled as iPPSDn+1.

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Table 1: Former classification of PHP along with the other disorders affecting the PTH/PTHrP signalling pathway; note the overlap of phenotypes and molecular defects of the patients. Diseases included in the former classification are PHP1A, PHP1B, PHP1C and PPHP.

	PHP1A	PHP1C	PHP1B					
Clinical presentation	AHO	AHO	No AHO	AHO in some patients (brachydactyly, subcutaneous ossification) and/or obesity	AHO in very few patients	Mental retardation reported in 2 patients, lambdoid synostosis, early-onset obesity, macrocephaly	BWS	No AHO
	Obesity	Obesity	No obesity		Obesity may be present		Obesity	no obesity
	Cognitive impairment	Cognitive impairment	No Cognitive impairment					
	Subcutaneous ossifications	Subcutaneous ossifications						
Hormone resistance	Resistance to PTH, TSH, GHRH, calcitonin, epinephrine, glucagon and gonadotropins	Resistance to PTH, TSH, epinephrine and gonadotropins	PTH resistance	PTH resistance, ± TSH resistance	PTH resistance, ± TSH resistance	PTH resistance, ± TSH resistance	PTH resistance	PTH resistance, ± TSH resistance
In vitro activity of Gsa	Significantly below controls	Similar to controls	Similar to controls	Mildy decreased when compared to controls	Mildy decreased when compared to controls			Similar to controls
LOI at the GNAS DMRs				LOM at the GNAS A/B:TSS-DMR	Broad LOI	Broad LOI	Broad LOI	Broad LOI
Genetic lesion	Heterozygous mutation in the coding sequence of GNAS (maternal allele)	Heterozygous mutation in the coding sequence of GNAS (p.E392K, p.E392X, p.L388R and p.Y391X, all in exon 13) (maternal allele)	Heterozygous mutation in the coding sequence of GNAS (p.Ile382del) (maternal allele)	Recurrent 3-kb STX16 deletion or 4.2-kb deletion of STX16	unknown	UPD(20)pat including GNAS	MLID	Maternal deletion of NESP and/or AS or Duplication of GNAS
References	(32–39)	(29,30,78)	(112)	(50–52,113)	(50,51,63,74)	(59–63)	(114)	(53,54,58,115)

	PPHP		POH	2q37.3 Deletion Syndrome	PHP2	Acrodysostosis			Blomstrand dysplasia	Eiken disease
Clinical presentation	AHO Subcutaneous ossifications	AHO Subcutaneous ossifications	Subcutaneous ossifications	AHO Cognitive impairment	No AHO Hypocalcemia, osteomalacia	Severe AHO Cognitive impairment in some patients	AHO	Severe AHO Hypertension	Lethal dwarfism	Epiphyseal dysplasia Short stature
Hormone resistance	No	Mild	No	No	PTH resistance	PTH resistance, and TSH in some patients	PTH resistance, and TSH in some patients	No		Elevated PTH in one patient
In vitro activity of Gsa	Significantly below controls	Significantly below controls								
LOI at the GNAS DMRs										
Genetic lesion	Heterozygous mutation in the coding sequence of GNAS (paternal allele)	Heterozygous mutation in the coding sequence of GNAS (paternal allele)	Heterozygous mutation in the coding sequence of GNAS (paternal allele) or no mutation identified	Deletion of the 2q37.3 chromosomal region including HDAC4	None	Heterozygous mutation in the coding sequence of PRKAR1A or PDE4D	Heterozygous mutation in the coding sequence of PRKAR1A	Heterozygous mutation in the coding sequence of PDE3A	Biallelic inactivating mutation in the coding sequence of PTH1R	Biallelic inactivating mutation in the coding sequence of PTH1R
References	(34,36,44,100)	(77)	(39,45,46,79,80)	(116)	(14)	(16,82,90,91,117–120)	(90,91)	(92)	(9,11)	(10)

Legend: PHP, pseudohypoparathyroidism; PPHP, Pseudopseudohypoparathyroidism; AHO, Albright's hereditary osteodystrophy; BWS: Beckwith-Wiedemann syndrome; MLID: multilocus imprinting defect; NA, not available.

Table 2: Non exhaustive review of classifications used in other conditions

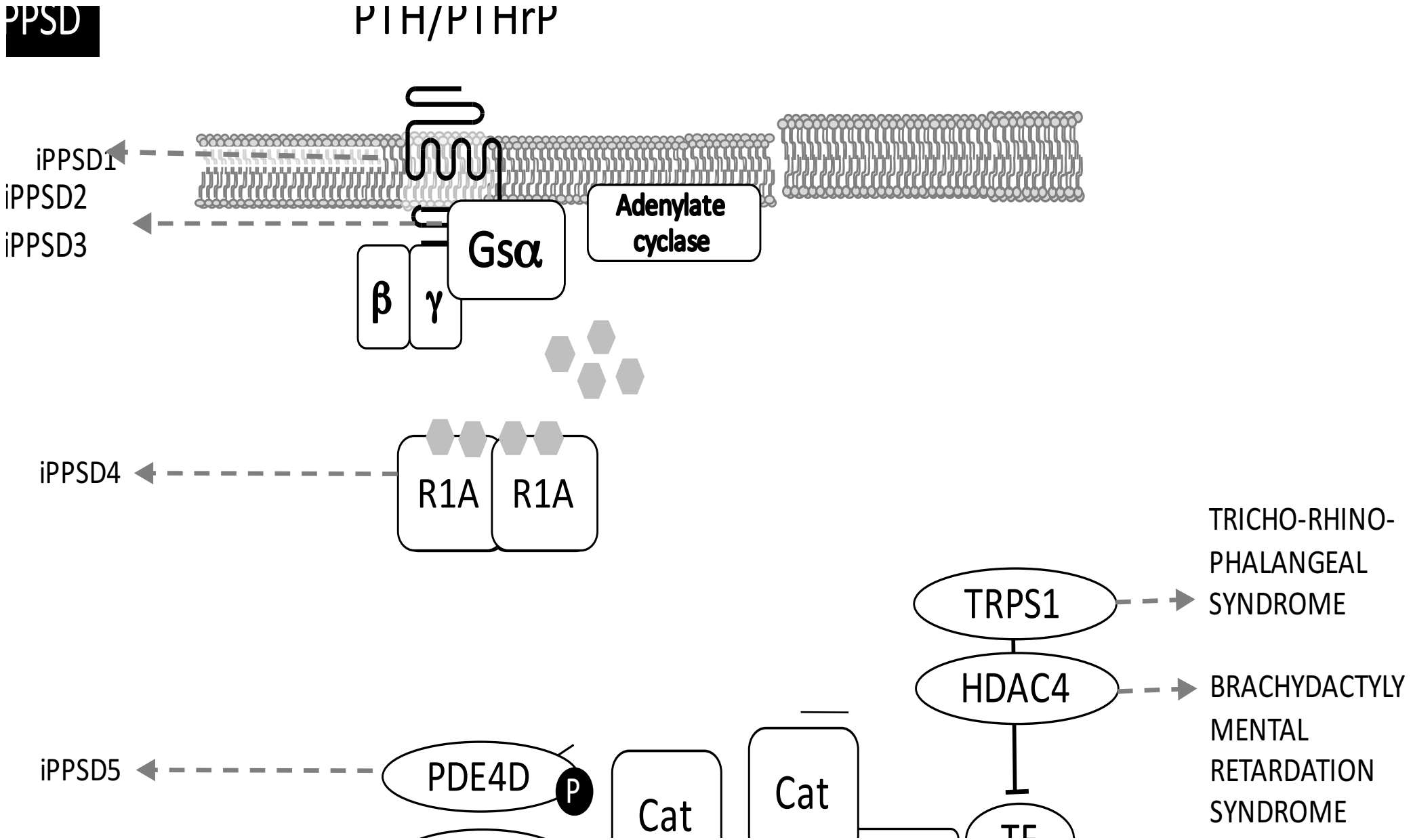
	Methodology used to build the classification	Mode of classification	Advantages	Limitations
Primary Immunodeficiency Diseases (69)	2-days meeting	Groups of diseases according to the most fundamental defect Presented as a table format	Allows a practical clinical framework for PID diagnosis	The complexities of these conditions cannot easily be captured in the limited table format
Skeletal dysplasia (66)	Meeting, extensive review of the literature, and circulation of drafts of the manuscript	Groups of diseases defined by molecular, biochemical and/or radiographic criteria	Disorders are caused by disturbances in related metabolic pathways or gene networks, Sheer number of conditions included	The "hybrid" nature of the classification, not clinical, not molecular
Autosomal dominant tubule interstitial kidney disease (67)	Meeting, agreement on the manuscript	Agreement on a novel name: ADTKD Classification based on the underlying genetic defect: ADTKD-gene	Provide information on the disease	Use in communication with patients may not be easy
Endocrine diseases (68)	Literature review	Groups of diseases by organ		
Diabetes mellitus (MODY) (70)	Meetings, agreement on the manuscript	Groups of diabetes by diseases' mechanism	Provide information on the disease mechanism Allow numbering of new diabetes after identification of new genes for MODY (MODY1, MODY2, MODY3, MODY4, …)	Very large groups of disease (type 2 diabetes for example)
Osteogenesis Imperfecta (64)	Literature review	Phenotypes on evolution, radiology, clinics and genetics	Provide information on the disease mechanism and genetics	Confusing as one causing gene may be in different categories

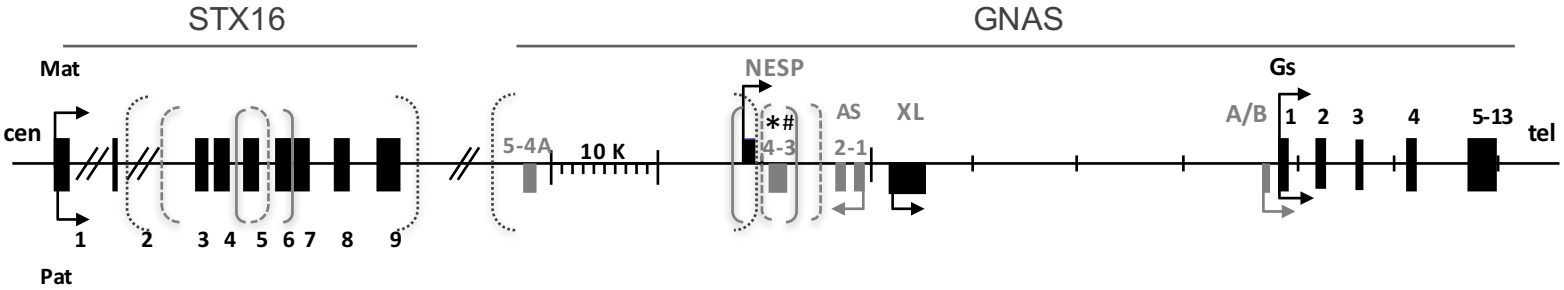
Table 3: Definition of major and minor criteria for iPPSD and differential diagnoses

		Assessment	Differential diagnosis	References
I. MAJOR CRITERIA	1. PTH resistance	Ionized calcium, total calcium Phosphate Magnesium PTH Vitamin D (25OHD) Creatinine Urinary calcium Urinary phosphate PTH infusion test in challenging cases	Normocalcemic hyperparathyroidism Renal failure Vitamin D deficiency or any kind of secondary hyperparathyroidism	(16)
	2. Ectopic ossification	Detailed physical exam X-rays	Fibrodysplasia Ossificans Progressiva (FOP, OMIM# 135100), Post-traumatic Osteoma Cutis	
	3. Brachydactyly type E (comprises the IV)	Clinical inspection (fist), Hand and feet X-rays	Turner syndrome, Tricho-rhino-phalangeal syndrome (TRPS), TRPS I, (OMIM#190350), TRPS-II (OMIM#150230) and TRPS-III, (OMIM#190351)	
II. MINOR CRITERIA	1. TSH resistance	TSH, T4l, Antibodies, Imaging[1]	Mutations in the TSH receptor	(26,27)
	2. Other hormonal resistances	IGF-1 (GH stimulation test if necessary), Calcitonin, LH, FSH, GnRH test		(2,27,78,98–101)
	3. Motor and cognitive retardation or impairment	Computed tomography scan and/or MRI of the brain, Psychopathological rating scales adjusted for age		(24,25,34,85,86,102,116,117)
	4. Intrauterine and postnatal growth retardation	IUGR: Gestational age, birth weight, birth length, head circumference, comparison to reference charts; Post-natal growth: Growth charts, X-ray of the left hand for determination of the bone age		(16,40,92,103,104,121)
	5. Obesity/overweight	Weight SDS, BMI percentile, BMI z-score		(23,105,106)
	6. Flat nasal bridge and/or maxillar hypoplasia and/or round face	Clinical inspection		(4,84,86,90)
iPPSD CLINICAL DIAGNOSIS	a) Presence of one major criteria, either number 1 or 2; b) Presence of major criteria number 3 and at least 2 minor criteria[2]			

[1] US in adults with hypothyroidism and no evidence for autoimmunity; thyroid imaging through thyroid scintigraphy and US in neonates diagnosed through screening for congenital hypothyroidism.

[2] Minor criteria are nonspecific (obesity/cognitive impairment); for instance, the association of BDE + obesity or BDE + cognitive impairment would not be relevant for our classification. By raising the number of minor criteria from 1 to 2, we will reduce the risk of overdiagnosing patients with iPPSD.


PPSD
PTH/PTHrP
iPPSD1
iPPSD2
iPPSD3
Adenylate cyclase
Gsα
β
γ
iPPSD4
R1A
R1A
TRICHO-RHINO-PHALANGEAL SYNDROME
TRPS1
HDAC4
BRACHYDACTYLY MENTAL RETARDATION SYNDROME
iPPSD5
PDE4D
P
Cat
Cat


STX16
GNAS
Mat
cen
1
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3 4 5 6 7
8
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Pat
5-4A
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NESP
*#
4-3
AS
2-1
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A/B
Gs
1
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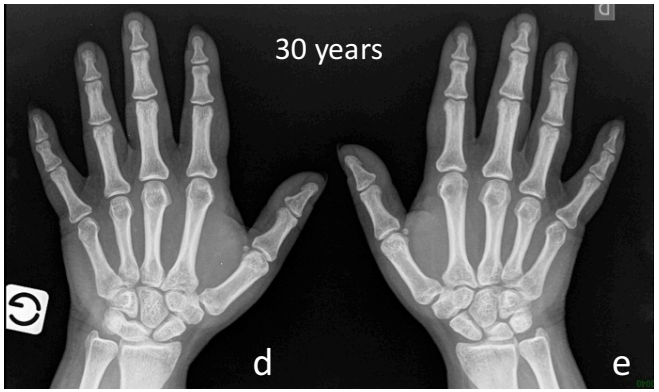
5-13
tel

Figure 2



PHP1A	PHP1A	PPHP
GNAS (p.W154X)	*GNAS* (p.Asp190MetfsX14)	*GNAS* (p.Asp190MetfsX14)
iPPSD2	iPPSD2	iPPSD2

PHP1B	PHP1B	ACRDYS	ACRDYS	ACRDYS
del STX16	Broad LOI	*PRKAR1A* (p. R368X)	*PRKAR1A* (p.T239A)	*PDE4D*
iPPSD3	iPPSD3	iPPSD4	iPPSD4	iPPSD5

Figure 3

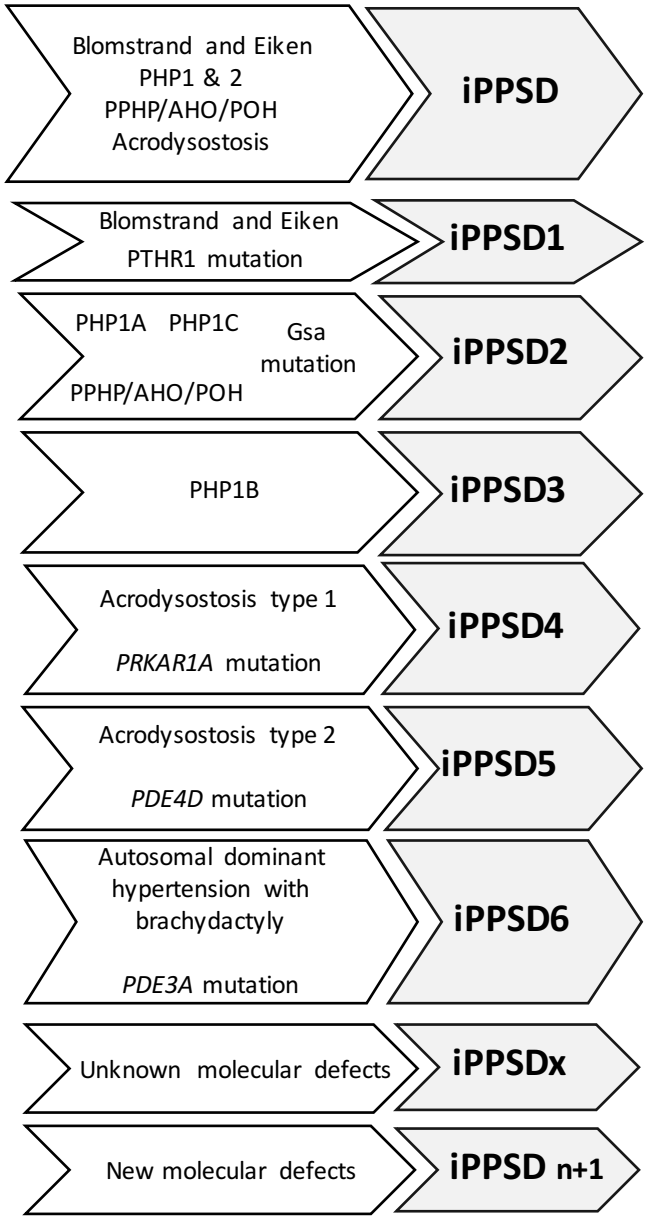

Blomstrand and Eiken
PHP1 & 2
PPHP/AHO/POH
Acrodysostosis
iPPSD
Blomstrand and Eiken
PTHR1 mutation
iPPSD1
PHP1A PHP1C
Gsa
mutation
PPHP/AHO/POH
iPPSD2
PHP1B
iPPSD3
Acrodysostosis type 1
PRKAR1A mutation
iPPSD4
Acrodysostosis type 2
PDE4D mutation
iPPSD5
Autosomal dominant
hypertension with
brachydactyly
PDE3A mutation
iPPSD6
Unknown molecular defects
iPPSDx
New molecular defects
iPPSD n+1

Figure 4